IN THE MATTER OF an
Application for an Swiss Patent
in the name of
Solvias AG
filed under N° 0624/03
and
IN THE MATTER OF an
Application for an US Patent

We, **Solvias AG**, do hereby certify to the best of our knowledge, information and belief that the annexed specification is a true and complete translation in English of Swiss priority document N° 0624/03 filed on April 7, 2003.

Solvias AG

For Solvias AG
Name(s): Dr. Mario Grenz
Title(s): Patent Attorney

[Shield]

SWISS CONFEDERATION

Certificate

The attached documents agree with the original technical documents of the Patent Application for Switzerland and Liechtenstein characterized on the next page. Switzerland and the Duchy of Liechtenstein constitute a single territory of protection. Hence, protection can only be requested for both countries conjointly.

Berne, February 11, 2004

Federal Institute of Intellectual Property

Patent administration

[signature]
Heinz Jenni

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Federal Institute of
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Certificate of deposition for Patent Application No. 2003 0624/03 (Art. 46 para. 5 PatV)

The Federal Institute for Intellectual Property certifies the entry of the Swiss patent application identified below.

Title:
Amine-substituted diphenyldiphoshines

Applicant:
Solvias AG
Klybeckstrasse 191
4057 Basel

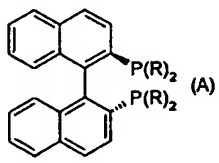
Date of filing: April 7, 2003

Prospective classes: C01G, C07B, C07F

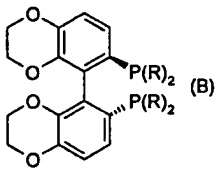
Amine-substituted diphenyldiphosphines

The present invention relates to diphenyldiphosphines having at least one amine substituent in the para position relative to the phosphine group, metal complexes with these diphosphines as catalysts for enantioselective syntheses and the use of the metal complexes for enantioselective syntheses.

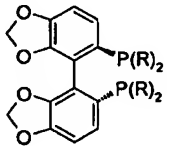
Chiral biaryl-1,1'-diphosphines are an important class of ligands for metal complexes as catalysts for enantioselective syntheses. Ruthenium and rhodium complexes have been found to be particularly useful for enantioselective hydrogenation and rhodium complexes have been found to be particularly useful for enantioselective isomerizations. Some examples of known chiral biaryl-1,1'-diphosphines as ligands in metal complexes are BINAP (cf. S. Akutagawa, Applied Catal. A: General 128 (1995) 171) of the formula (A), BisbenzodioxanPhos (C.-C. Pai, Y.-M. Li, Z.-Y. Zhou, A.S.C. Chan, Tetrahedron Lett., 43 (2002) 2789) of the formula (B), and diphosphines of the formula (C) described in EP-A-0 850 945:



(A)

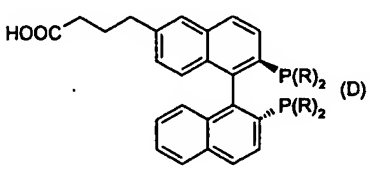


(B)

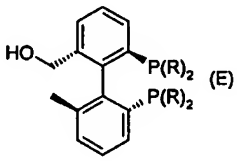


(C).

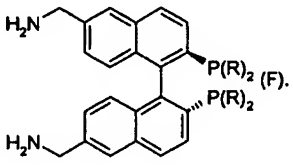
Mention may also be made of the following examples of functionalized biaryldiphosphine ligands of the formulae (D), (E) and (F); see D. J. Bayston, J. L. Fraser, M. R. Ashton, A. D. Baxter, E. C. Polywka, E. Moses, J. Org. Chem., 63 (1998) 3137, for the formula (D); EP-A-1 002 801 for the formula (E); R. ter Halle, B. Colasson, E. Schulz, M. Spagnol, M. Lemaire, Tetrahedron Lett., 41 (2000) 643, for the formula (F):



(D)



(E)



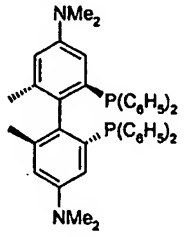
(F).

Ligands of this type can easily be covalently bound to a support or absorbed on a support by means of the functional groups -COOH, -OH or $-NH_2$, which makes them easier to be

separated off and makes reuse possible. However, a disadvantage of the ligands described hitherto in the literature is that their catalytic properties can be influenced only via the choice of the radicals bound to the phosphorus.

Although a relatively broad spectrum of ligands of the biaryldiphosphine type is already known as a result, there is still a need for improvements in respect of synthesis, catalytic properties (activity, productivity, enantioselectivity), ability for particular base structures to be finely adjusted by variation of the radicals on the base structure (tuning) or handling. Since the present-day state of knowledge does not make it possible to predict which ligand will give the best results for a given substrate without experimentation, it would be of interest in industry to have a very broad range of different ligands available in order to determine optimal ligands for a particular substrate experimentally.

Only a few chiral biphenyldiphosphines having amine groups bound directly to the benzene rings have hitherto become known, since they are difficult to synthesize. In addition, anilinic compounds are regarded as unstable since they can be decomposed oxidatively, which is regarded as troublesome both in respect of intermediates for the synthesis and in respect of the amino-substituted biphenyldisphosphines. Their catalytic properties, too, have not yet been examined. The only known compound which has been prepared hitherto (R. Schmid, M. Cereghetti, B. Heiser, P. Schönholzer, H.J. Hansen, Helv. Chim. Acta, 71 (1988) 897) is the ligand of the formula (G)



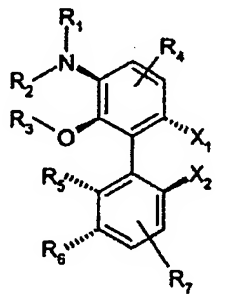
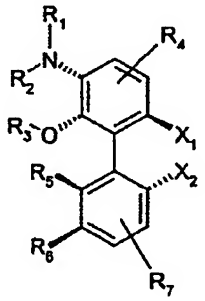
(G).

However, the electronic properties of the phosphine groups located in the catalytic center of the metal complexes can be influenced only slightly by the dimethylamine group bound in the meta positions. It is extremely desirable to have biphenyldiphosphines substituted by amine groups in which the electronic properties on the phosphorus atoms and thus the catalytic properties of the metal complexes can be influenced in a targeted manner, for example by substitution of the N atoms or by salt formation, available as ligands.

However, for the above reasons, it is not possible to foresee whether diphenyldiphosphines having an amino group in the para position relative to the phosphine can be prepared and are sufficiently stable as ligands in metal complexes in order to be able to be used in catalytic reactions.

It has now surprisingly been found that biaryldiphosphine ligands having at least one amino group in the para position relative to the phosphine group can be prepared and are sufficiently stable to be able to be used in catalysis. In addition, it has been found that the electronic properties of the ligands can be altered in a simple fashion and optimized for particular substrates with the aid of the amino group, e.g. by salt formation or by variation of the substituents on the nitrogen atom.

The present invention provides compounds of the formula I,


(I),

(Ia),

where

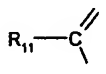
X_1 and X_2 are each, independently of one another, secondary phosphino;

R_1 and R_2 are each, independently of one another, hydrogen, C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_6-C_{10}-aryl or C_7-C_{11}-aralkyl, or

R_1 and R_2 together are C_4-C_8-alkylene, 3-oxapentyl-1,5-ene, $-(CH_2)_2-NH-(CH_2)_2-$ or $-(CH_2)_2-N(C_1-C_4alkyl)-(CH_2)_2-$,

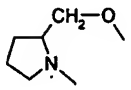
R_3 is hydrogen, C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_6-C_{10}-aryl or C_7-C_{11}-aralkyl, or

R_1 is as defined above and R_2 and R_3 together are C_2-C_8-alkylidene, C_4-C_8-cycloalkylidene, C_1-C_4-alkylene, C_2-C_8-alk-1,2-enyl, -C(O)- or a group of the formula



or

R_1R_2N and R_3O together are a group of the formula



R_4 and R_7 are each, independently of one another, hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, F, Cl or trifluoromethyl,

R_5 is hydrogen, R_4 or an R_3O- group, where R_3O- groups in the two rings can be identical or different,

R_6 is hydrogen, R_7 or an R_1R_2N- group, where R_1R_2N- groups in the two rings can be identical or different,

R_5 and R_6 together are trimethylene, tetramethylene or –CH=CH-CH=CH-,

and

R_{11} is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_6-C_{10}-aryl or C_7-C_{11}-aralkyl,

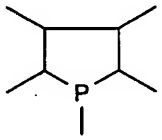
where R_1, R_2, R_3, R_4 and R_7 are unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, OH, F, Cl, Br, trifluoromethyl, C_1-C_4-hydroxyalkyl, -COOH, $-SO_3H$, -C(O)O-C_1-C_4-alkyl, $-SO_3$-C_1-C_4-alkyl, -C(O)-NH_2, -CONHC_1-C_4-alkyl, -CON(C_1-C_4-alkyl)$_2$, $-SO_3-NH_2$, $-SO_2$-NHC_1-C_4-alkyl, $-SO_3$-N(C_1-C_4-alkyl)$_2$, $-O_2C-R_8$, $-O_3S-R_8$, -NH-(O)C-R_8, -NH-O_3S-R_8, $-NH_2$, $-NHR_9$ or $-NR_9R_{10}$, where R_8 is hydrogen, C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_6-C_{10}-aryl or C_7-C_{11}-aralkyl, and R_9 and R_{10} are each, independently of one another, C_1-C_4-alkyl, phenyl or benzyl or R_9 and R_{10} together are tetramethylene, pentamethylene, 3-oxa-1,5-pentane or -$(CH_2)_2$-N(C_1-C_4-alkyl)-$(CH_2)_2$-.

One group of preferred substituents is C_1-C_4-alkyl, C_1-C_4-alkoxy, F, trifluoromethyl, hydroxymethyl, hydroxyethyl, -COOH, $-SO_3H$, -C(O)O-methyl or -ethyl, $-SO_3$-methyl or -ethyl, -C(O)-NH_2, -CONHC_1-C_4-alkyl, -CON(C_1-C_4-alkyl)$_2$, $-SO_3-NH_2$, $-SO_2$-NHC_1-C_4-alkyl, $-SO_3$-N(C_1-C_4-alkyl)$_2$, $-O_2C-R_8$, $-O_3S-R_8$, -NH-(O)C-R_8, -NH-O_3S-R_8 or $-NR_9R_{10}$, where R_8 is C_1-C_4-alkyl, C_5-C_6-cycloalkyl, C_5-C_6-cycloalkyl-C_1-C_4-alkyl, phenyl, naphthyl, benzyl or phenylethyl, and R_9 and R_{10} are each, independently of one another, C_1-C_4-alkyl, phenyl or benzyl. The alkyl can be, for example, methyl, ethyl, n- or i-propyl and n-, i- or t-butyl.

The radicals R_1, R_2, R_3, R_4, R_5, R_6 and R_7 can contain chiral carbon atoms, which can prove to be particularly advantageous in the separation of the optical isomers, since diastereomers are often easier to separate by chromatography.

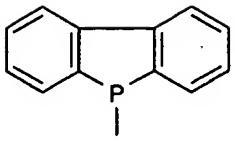
The individual phosphine groups X_1 and X_2 can contain monovalent hydrocarbon radicals, or the two hydrocarbon radicals together with the P atom can form a 3- to 8-membered ring. The individual phosphine groups X_1 and X_2 preferably contain two identical hydrocarbon radicals, with X_1 and X_2 being able to be different from one another. The hydrocarbon radicals can be unsubstituted or substituted and can have from 1 to 22, preferably from 1 to 12, carbon atoms. Among the compounds of the formulae I and Ia, particular preference is given to those in which the individual phosphine groups are two identical radicals selected from the group consisting of linear or branched C_1-C_{12}-alkyl; unsubstituted or C_1-C_6-alkyl- or C_1-C_6-alkoxy-substituted C_5-C_{12}-cycloalkyl or C_5-C_{12}-cycloalkyl-CH_2-; phenyl or benzyl; and phenyl or benzyl substituted by halogen (for example F, Cl and Br), C_1-C_6-alkyl, C_1-C_6-haloalkyl (for example trifluoromethyl), C_1-C_6-alkoxy, C_1-C_6-haloalkoxy (for example trifluoromethoxy), $(C_6H_5)_3Si$, $(C_1$-C_{12}-alkyl$)_3Si$, secondary amino or CO_2-C_1-C_6-alkyl (for example $-CO_2CH_3$).

Examples of secondary phosphine groups in which the two hydrocarbon radicals together with the P atom form a 3- to 8-membered ring are, in particular, those of the formula

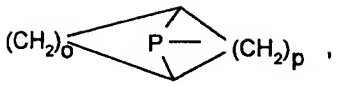


These phosphine groups are phospholanes in which the two radicals in the phosphine groups X_1 and X_2 together are, for example, unsubstituted or halogen-, C_1-C_6-alkyl- or C_1-C_6-alkoxy-substituted tetramethylene (or pentamethylene). The substituents are preferably located in the two ortho positions relative to the P atom, with the substituents bound to the carbon atoms being able to be hydrogen, C_1-C_4-alkyl, phenyl, benzyl, C_1-C_4-alkoxy, phenyloxy or benzyloxy. Furthermore, two adjacent substituents on carbon can also be C_1-C_4-alkylidenedioxyl.

The phosphine groups can also be groups of the formula



or



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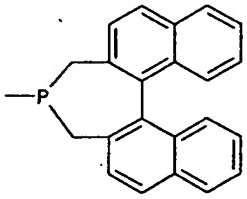
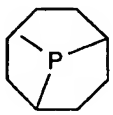


or

where o and p are each, independently of one another, an integer from 2 to 10 and the sum of o+p is from 4 to 12, preferably from 5 to 8, and the phenyl rings are unsubstituted or substituted by C_1-C_4-alkyl or C_1-C_4-alkoxy. Examples are [3.3.1]phobyl and [4.2.1]phobyl of the formulae



Examples of alkyl substituents on P, which preferably contain from 1 to 6 carbon atoms, are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl and the isomers of pentyl and hexyl. Examples of unsubstituted or alkyl-substituted cycloalkyl substituents on P are cyclopentyl, cyclohexyl, methylcyclohexyl and ethylcyclohexyl and dimethylcyclohexyl. Examples of alkyl-, alkoxy-, haloalkyl-, haloalkoxy-substituted phenyl and benzyl substituents on P are methylphenyl, dimethylphenyl, trimethylphenyl, ethylphenyl, methylbenzyl, methoxyphenyl, dimethoxyphenyl, trifluoromethylphenyl, bistrifluoromethylphenyl, tristrifluoromethylphenyl, trifluoromethoxyphenyl, bistrifluoromethoxyphenyl, dimethylaminophenyl, 3,5-di-t-butylphen-1-yl, 3,5-di-t-butyl-4-methoxyphen-1-yl, 3,5-di-t-butyl-4-dimethylaminophen-1-yl, 3,5-di-i-propylphen-1-yl, 3,5-di-i-propyl-4-methoxyphen-1-yl, 3,5-di-i-propyl-4-dimethylaminophen-1-yl, 3,5-di-methyl-4-methoxyphen-1-yl, 3,5-di-methyl-4-dimethylaminophen-1-yl and 3,4,5-trimethoxyphen-1-yl.

Preferred phosphine groups are those containing identical radicals selected from the group consisting of C_1-C_6-alkyl, unsubstituted cyclopentyl or cyclohexyl or cyclopentyl or cyclohexyl substituted by from 1 to 3 C_1-C_4-alkyl or C_1-C_4-alkoxy groups, benzyl; and in particular phenyl which is unsubstituted or substituted by from 1 to 3 C_1-C_4-alkyl, C_1-C_4-alkoxy, (C_1-C_4-alkyl)$_2$N-, F, Cl, C_1-C_4-fluoroalkyl or C_1-C_4-fluoroalkoxy groups.

In the compounds of the formulae I and Ia, X_1 is preferably a -P(R)$_2$ group and X_2 is preferably a -P(R')$_2$ group, where R and R' are each, independently of one another, a hydrocarbon radical which has from 1 to 20 carbon atoms and is unsubstituted or substituted by halogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, -CO_2-C_1-C_6-alkyl, (C_1-C_4-alkyl)$_2$N-, (C_6H_5)$_3$Si or (C_1-C_{12}-alkyl)$_3$Si; or the radicals R and R' together are unsubstituted or C_1-C_4-alkyl- and/or C_1-C_4-alkoxy-substituted tetramethylene or pentamethylene.

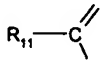
Preference is given to R and R' being identical radicals selected from the group consisting of branched C_3-C_6-alkyl, unsubstituted cyclopentyl or cyclohexyl or cyclopentyl or cyclohexyl substituted by from one to three C_1-C_4-alkyl or C_1-C_4-alkoxy groups, unsubstituted benzyl or benzyl substituted by from one to three C_1-C_4-alkyl or C_1-C_4-alkoxy groups and in particular unsubstituted phenyl or phenyl substituted by from one to three C_1-C_4-alkyl, C_1-C_4-alkoxy, -NH_2, (C_1-C_4-alkyl)NH-, (C_1-C_4-alkyl)$_2$N-, OH, F, Cl, C_1-C_4-fluoroalkyl or C_1-C_4-fluoroalkoxy groups.

R and R' are particularly preferably identical radicals selected from the group consisting of α-branched C_3-C_6-alkyl, unsubstituted cyclopentyl, cyclohexyl or cyclopentyl, cyclohexyl substituted by from one to three C_1-C_4-alkyl, C_1-C_4-alkoxy groups and unsubstituted phenyl or phenyl substituted by from one to three C_1-C_4-alkyl, C_1-C_4-alkoxy or C_1-C_4-fluoroalkyl groups.

R_1 and R_2 are each preferably independently of one another, a substituent on the N atom, for example C_1-C_4-alkyl, C_5-C_6-cycloalkyl, C_5-C_6-cycloalkyl-C_1-C_2-alkyl, phenyl or benzyl. R_1 and R_2 together are preferably C_4-C_5-alkylene, 3-oxapentyl-1,5-ene or -(CH_2)$_2$-N(methyl)-(CH_2)$_2$-. Some examples are methyl, ethyl, propyl, n-butyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, tetramethylene, pentamethylene, phenyl and benzyl.

R_3 is preferably a substituent on the O atom, for example C_1-C_4-alkyl, C_5-C_6-cycloalkyl, C_5-C_6-cycloalkyl-C_1-C_2-alkyl, phenyl or benzyl. Some examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, cyclopentyl, cyclohexyl and cyclohexylmethyl.

R_1 is preferably a substituent on the N atom and R_2 and R_3 are preferably together C_2-C_4-alkylidene, C_5-C_6-cycloalkylidene, C_1-C_2-alkylene, C_2-C_4-alk-1,2-enyl, -C(O)- or a group of the formula

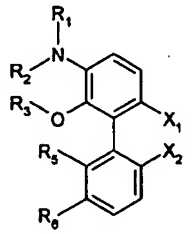


where R_{11} is preferably C_1-C_4-alkyl, C_5-C_6-cycloalkyl, C_5-C_6-cycloalkylmethyl, phenyl or benzyl. Some examples of R_2 and R_3 together are ethylidene, propylidene, butylidene, cyclohexylidene, benzylidene, methylene, 1,2-ethylene, 1,2-ethenylene, 1,2-propenylene and 1,2-butenylene.

Some examples of R_{11} are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, phenyl and benzyl.

R_4 and R_7 are preferably each hydrogen. When R_4 and R_7 are substituents, these are preferably C_1-C_2-alkyl, C_1-C_2-alkoxy, F, Cl or trifluoromethyl.

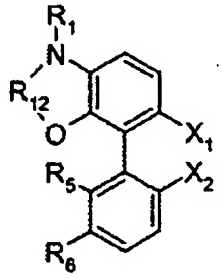
In a preferred embodiment, the diphenyldiphosphines of the invention correspond to the formula Ib,



(Ib)

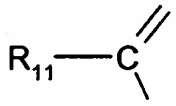
where R_1, R_2 and R_3 are each, independently of one another, C_1-C_4-alkyl, preferably methyl or ethyl, R_5 is hydrogen or an OR_3 group, R_6 is hydrogen or an NR_1R_2 group, or R_5 and R_6 together are –CH=CH-CH=CH-, and X_1 and X_2 are each secondary phosphino. The abovementioned embodiments and preferences apply to X_1 and X_2.

In another preferred embodiment, the diphenyldiphosphines of the invention correspond to the formula Ic,



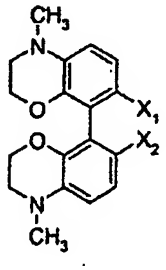
(Ic)

where R_1 is C_1-C_4-alkyl, preferably methyl or ethyl, R_5 and R_6 are each hydrogen or R_5 and R_6 together are an -NR_1-R_{12}-O- group, X_1 and X_2 are each secondary phosphino, and R_{12} is 1,2-ethylene, 1,2-ethenylene, -C(O)- or a group of the formula

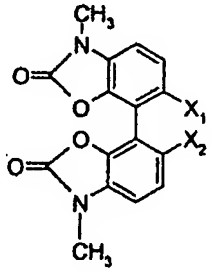


where R_{11} is branched C_3-C_8-alkyl, C_5-C_6-cycloalkyl, phenyl or benzyl. The abovementioned embodiments and preferences apply to X_1 and X_2.

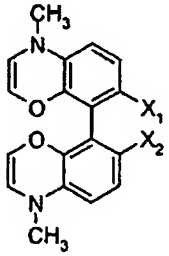
Some preferred specific compounds according to the invention correspond to the formulae Id, Ie, If, Ig and Ih,



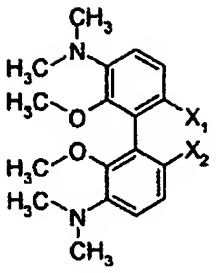
(Id)



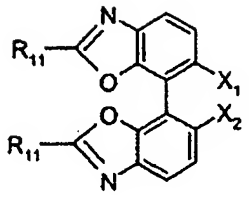
(Ie)



(If)



(Ig)



(Ih)

where R_{11} is phenyl or t-butyl, and X_1 and X_2 are as defined above, including the preferences. Preferred groups X_1 and X_2 are diphenylphosphino, dicyclohexylphosphino, and di-t-butylphosphino.

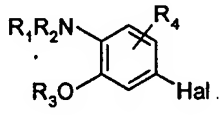
The compounds of the formula I can be prepared by methods which are known per se (Segphos synthesis) and are described in the references mentioned at the outset. Further details on the method of preparation may be found in:

[1] R. Schmid, E.A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Müller, M. Scalone, G. Schoettel and U. Zutter, Pure & Appl. Chem., 68 (1996) 131 - 388.

[2] EP 0 926 152 A1

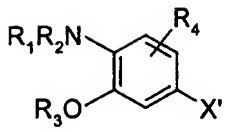
[3] H. Geissler in Transition Metals for Organic Synthesis (Eds.: M. Beller,C. Bolm), Wiley-VCH, Weinheim, 1998,158 – 183, and in the references mentioned in the publications.

it is possible to start out from, for example, compounds of the formula II

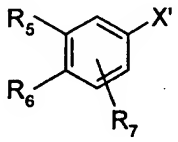


(II)

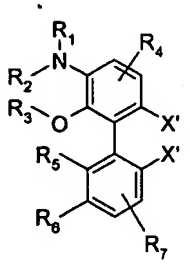
where R_1, R_2 and R_3 are as defined above, and react these firstly with a Grignard metal such as magnesium or lithium alkyl and then with a phosphine oxide of the formula RRP(O)-Hal or a phosphate halide of the formula $(R°O)_2P(O)$-Hal, where Hal is Cl, Br or I, R° is, for example, C_1-C_6-alkyl (methyl, ethyl) or phenyl and R is as defined above. Compounds of the formula II can also be reacted directly with $(R°O)_2P(O)$-Hal using Pd-catalyzed methods. Two equivalents of the resulting compound of the formula III for preparing symmetrical compounds,


(III),

where X' is RRP(O)- or $(R°O)_2P(O)$-, or one equivalent of a compound of the formula III and one equivalent of a compound of the formula IV which can be prepared as described in the first process step and in which R_5, R_6 and X' are as defined above, X' in the formula IV can be different from X' in the formula III,


(IV),

are reacted in the presence of a metal salt such as $CuCl_2$ or $FeCl_3$ to form compounds of the formula V

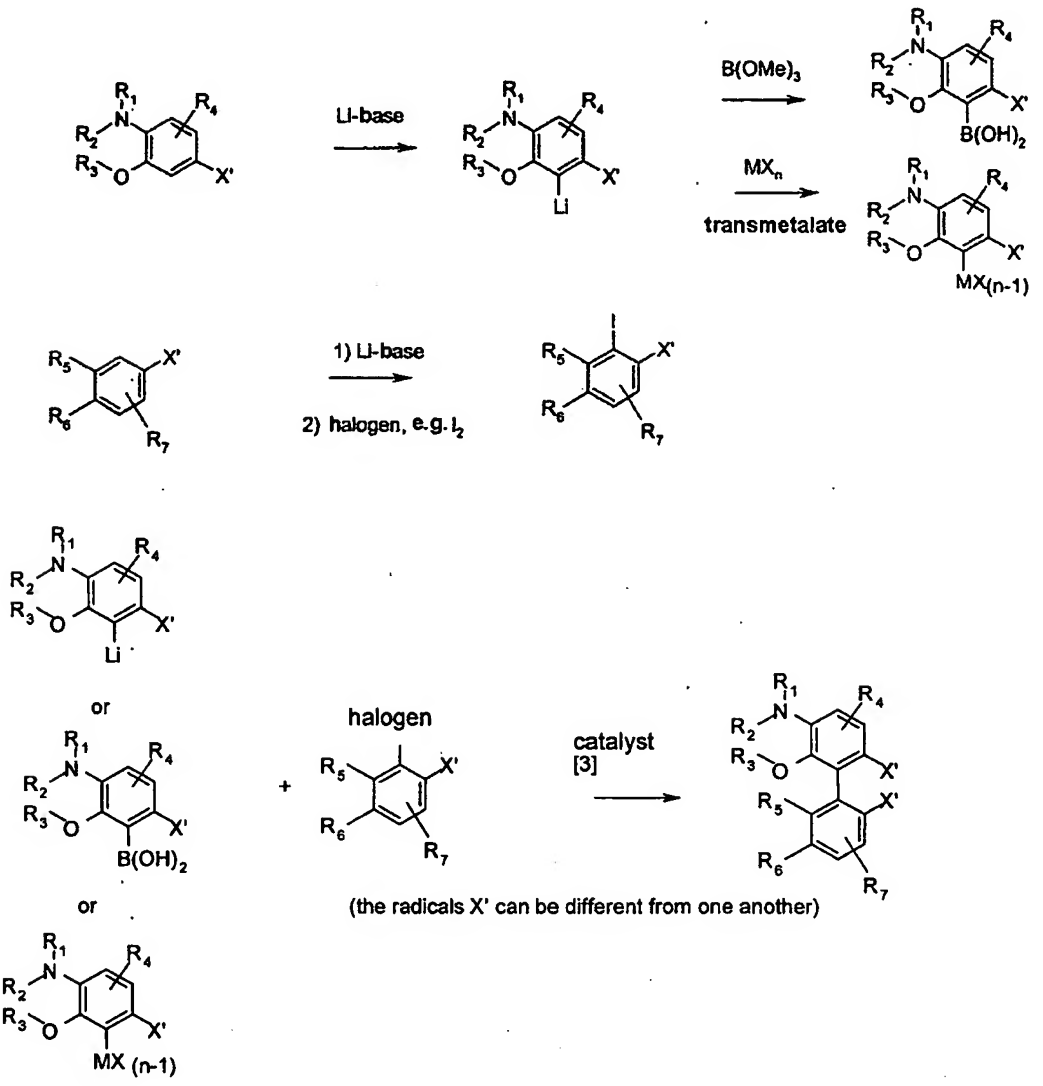

(V).

This synthesis also makes it possible to obtain compounds of the formulae I and Ia in which the groups X_1 and X_2 are different (R is different from R').

The reactions are advantageously carried out in suitable inert solvents such as ethers, nitriles, carboxamides or aromatic hydrocarbons. Suitable metal salts are, for example, halides of iron, cobalt and nickel, in particular iron(III) chloride and iron(III) bromide. Suitable bases are, for example, open-chain or cyclic, tertiary amines.

The preparation of both symmetrical and unsymmetrical compounds can also be carried out using catalytic coupling methods as described in [3]. For this purpose, the compounds of the

formulae III and IV are metalated or halogenated and subsequently coupled using catalytic methods, with R_5 preferably being hydrogen:



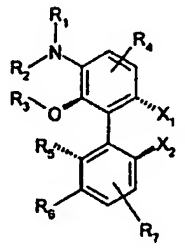
The compounds of the formula V can then be converted into the compounds according to the invention of the formula I in a manner known per se by means of reduction of the phosphine oxide group. As hydrogenating agents, it is possible to use metal hydrides, for example $Li(AlH_4)$. It is more advantageous to use alkylsilanes or chlorosilanes and alkylstannanes or chlorostannanes, for example trichlorosilane or trichlorostannane.

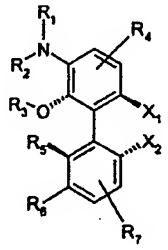
If R_1 to R_7 in the phosphine oxides of the formula V are not chiral radicals, the preparation generally gives racemates from which the desired enantiomers can be isolated by resolution by means of crystallization using a chiral auxiliary reagent or by chromatographic methods, with resolution advantageously being carried out using the compounds of the formula V. If a radical R_1 to R_7 is optically active, the diastereomers can be separated.

Phosphonate compounds V having nonchiral radical R_1-R_7 can be separated into their enantiomers by means of crystallization using a chiral auxiliary reagent or chromatographic methods in a manner similar to the phosphine oxide compounds V. The optically pure or optically enriched phosphonate compounds are subsequently converted into the desired phosphine oxides by known methods [1] by means of reaction with Grignard reagents R-Mg-X and finally reduced as described above to give compounds of the formulae I and Ia.

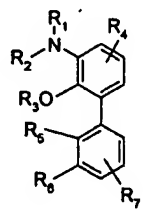
The novel compounds of the formula I can also be prepared by a novel process in which halogenation and introduction of the phosphine group are carried out before the coupling reaction to form the biphenyl skeleton. Surprisingly, the halogenation proceeds so regioselectively that high yields can be achieved.

The invention further provides a process for preparing compounds of the formulae I and Ia,


(I),

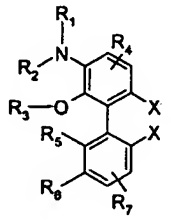

(Ia),

where R_1, R_2, R_3, R_4, R_5, R_6, R_7, X_1 and X_2 are as defined above, which comprises the steps:
a) halogenation of a compound of the formula VI


(VI),

where R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are as defined above, or R_1 is a protective group which can be split off and R_2 is hydrogen or is as defined above, or R_3 is a protective group which can be split off, or R_1 and R_3 form a protective group which can be split off and R_2 is hydrogen or is as defined above,

by means of chlorine, bromine or iodine to form a compound of the formula VII

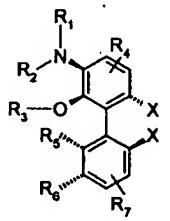


(VII),

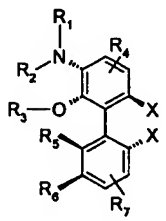
where X is chlorine, bromine or iodine,

b) if appropriate to introduce the radicals R_2 and R_3, removal of the protective groups to form OH-functional and NH-functional groups and replacement of the H atoms in the OH-functional and NH-functional groups by means of a reagent R_2-X_2, R_3-X_2 or X_2-R_{13}-X_2, where X_2 is a leaving group and R_{13} is 1,2-alkylene or 1,2-cycloalkylene, to produce compounds of the formula VII, and

if appropriate resolution of the racemates of the formula VII (by known methods such as crystallization using a chiral auxiliary reagent or chromatographic methods using chiral columns)

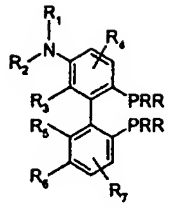


VIIa



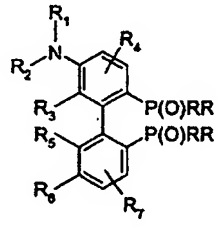
VIIb

c) metalation of the compounds of the formula VII, for example by means of a lithium alkyl, and subsequent reaction with a halophosphine of the formula X_3-PRR (X_3 is halogen) in the presence of lithium alkyl to give diphosphines of the formula VIII, or with a halophosphine oxide of the formula X_3-P(O)RR to give diphosphine oxides of the formula IX, or with a phosphonate of the formula X_3-P(O)(OR°)$_2$ to give phosphonates of the formula IXa:

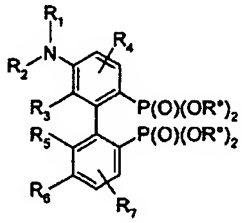


(VIII),

d) oxidation of the phosphine groups in compounds of the formula VIII by means of an oxidant to form compounds of the formula IX,

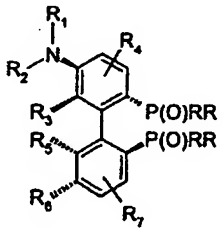


(IX)

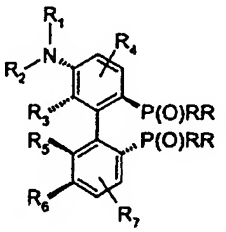


(IXa),

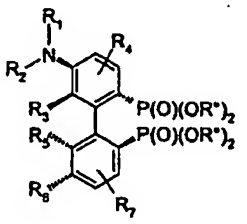
e) if a racemic starting material of the formula VII is used, resolution of the racemates of the formula VIII to give the enantiomers Ia and Ib, or resolution of the racemates of the formula IX to give the enantiomers of the formulae X and Xa, or resolution of the racemates of the formula IXa to give the enantiomers of the formulae Xb and Xc, and reaction of Xb and Xc with R-Mg-X to form phosphine oxides of the formula X and Xa,



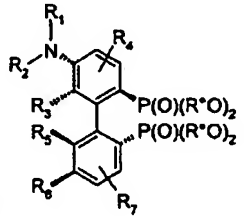
(X)



(Xa),

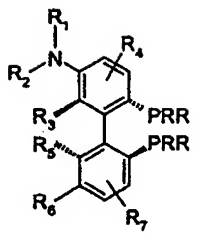


(Xb)

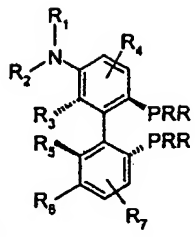


(Xc),

f) and reduction of the phosphine oxide group in the compounds of the formulae Xa and Xb to produce compounds of the formulae I and Ia.



(I)



(Ia).

The compounds of the formula VI can be prepared as follows. Commercially available 2,2'-dihydroxy-3,3'-dinitro-5,5'-dichlorobiphenyl (Niclofan) can be catalytically hydrogenated in a manner known per se by means of hydrogen and in the presence of hydrogenation catalysts, for example palladium or platinum, to form 2,2'-dihydroxy-3,3'-diaminobiphenyl (1). The H atoms of the hydroxy groups and one H atom of the amino group can be replaced by protective groups and the second H atom of the amino group can then be replaced by a radical R_2. The resulting compounds of the formula VI can be used in process step a).

As an alternative, the H atoms of the hydroxy groups and the H atoms of the amino group in the compounds (1) can be replaced by radicals R_1, R_2 and R_3 in a manner known per se. The resulting compounds of the formula VI can be used in process step a).

Methods and reagents for substituting OH and NH_2 groups are prior art and are illustrated in the examples. The introduction and removal of protective groups and methods and reagents for this purpose are also prior art and will not be described in more detail here. Suitable protective groups are, for example, radicals which form an ether bond, an ester bond, an amide bond, a carbonate bond, a carbamate bond or a urethane bond, which can easily be dissociated again either hydrolytically or hydrogenolytically. Suitable radicals can correspond to the formula

$$R_{14}\text{-}(X_4)_x\text{-}(X_5)_y\text{-}$$

where R_{14} is an aliphatic, cycloaliphatic, aromatic or araliphatic radical having from 1 to 8 carbon atoms, X_4 is -O-, -NH- or -N(C_1-C_4-alkyl), X_5 is -C(O)- or -SO_2- and x and y are each, independently of one another 0 or 1. If R_1 and R_3 form a protective group, this can be, for example, -C(O)-. Further examples of protective groups are acetate, trichloroacetate, triflate, methylsulfonate, tosylate, benzyl, diphenylmethyl, trityl, trimethylsilyl, methoxycarbonyl and methylaminocarbonyl. It should be pointed out that protective groups

can at the same time be radicals R_1, R_2 and R_3 and are only replaced when other radicals R_1, R_2, and R_3 are to be introduced.

The reactions of process steps a) to d) and f) can be carried out without solvent or in inert solvents, with one solvent or mixtures of solvents being able to be used. Suitable solvents are, for example, aliphatic, cycloaliphatic and aromatic hydrocarbons (pentane, hexane, heptane, petroleum ether, cyclohexane, methylcyclohexane, benzene, toluene, xylene), aliphatic halogenated hydrocarbons (methylene chloride, chloroform, dichloroethane and tetrachloroethane), nitriles (acetonitrile, propionitrile, benzonitrile), ethers (diethyl ether, dibutyl ether, t-butyl methyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, tetrahydrofuran, dioxane, diethylene glycol monomethyl or monoethyl ether), ketones (acetone, methyl isobutyl ketone), carboxylic esters and lactones (ethyl or methyl acetate, valerolactone), N-substituted lactams (N-methylpyrrolidone), carboxamides (dimethylacetamide, dimethylformamide), acyclic ureas (dimethylimidazoline), sulfoxides and sulfones (dimethyl sulfoxide, dimethyl sulfone, tetramethylene sulfoxide, tetramethylene sulfone) and alcohols (methanol, ethanol, propanol, butanol, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, diethylene glycol monomethyl ether), nitromethane and water. Reactions with lithium alkyl are mainly carried out in alphatic or aromatic hydrocarbons or ethers.

The reactions of process steps a) to d) and f) can be carried out with cooling or heating, for example in a range from -100°C to 200°C, preferably from -60 to 150°C. The temperatures to be employed in the individual reactions are known to those skilled in the art and can be taken from the examples.

The halogenation of process step a) is advantageously carried out in the presence of Lewis acids, for example metal halides such as $FeCl_3$ or $FeBr_3$, which can also be generated in situ.

The hydrolytic removal (process step b) of protective groups in a basic or acid reaction medium is known. In general, alkali metal hydroxides such as NaOH or KOH and mineral acids such as hydrochloric acid or sulfuric acid are used. The hydrogenolytic removal is generally carried out using hydrogen in the presence of noble metals such as platinum or palladium as catalysts. The haloaminobisphenols obtained are not very stable and are advantageously not isolated but used directly in the subsequent reactions for reaction with

reagents R_1-X_2, R_2-X_2, R_3-X_2 or X_2-R_{13}-X_2. The reagents are reagents for introducing alkyl, cycloalkyl, cycloalkylalkyl and aralkyl groups. Leaving groups in such reagents are known. They are mostly halogen such as chlorine, bromine or iodine, or an acid radical such as sulfonate or sulfate.

Racemic compounds can be separated into their enantiomers by means of, for example, preparative chromatographic methods (for example HPLC) using chiral stationary phases.

The introduction of secondary phosphine groups to produce chiral diphosphine ligands for enantioselective catalysts according to process c) has been known for a relatively long time. As lithium alkyl, preference is given to using commercially available methyllithium or butyllithium. Process step c) gives ready-to-use diphosphine ligands, although these still have to be separated into the desired enantiomers if the resolution of the racemate has not previously been carried out at an earlier stage.

If it is simpler to carry out the resolution of the racemate via the phosphine oxides, the phosphine groups are oxidized according to process step d), because the phosphine oxides are considerably easier to separate into the enantiomers. Suitable oxidants are alkali metal peroxides and, in particular, hydrogen peroxide.

The resolution of the racemate at the stage of phosphonates has the advantage that various radicals can subsequently be introduced on the phosphorus virtually without racemization. The resolution of the racemate at the phosphonate stage by crystallization with suitable chiral auxiliary reagents is known. The conversion of phosphonates into phosphine oxides has likewise been described in the literature [1].

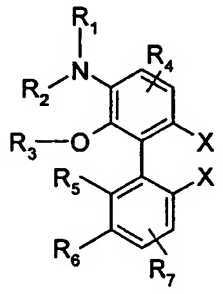
The resolution of the racemate according to process step e) can be carried out by known methods by means of crystallization in the presence of chiral complexing agents such as dibenzoyltartaric acid. Preparative separation by means of chromatographic methods (for example HPLC) using chiral stationary phases is also advantageous. Such columns having different chiral stationary phases are commercially available.

The reduction according to process step f) can be carried out using metal hydrides such as LiH, NaH, $Li(AlH_4)$, or by means of hydrosilanes or hydrostannanes, if appropriate under superatmospheric pressure. In the preferred reduction using hydrosilanes, for example

trichlorosilane, it is advantageous to add tertiary amines, for example trimethylamine or triethylamine. Up to equimolar amounts of these, based on the silane, can be used here.

The compounds of the formula I and their enantiomers are obtained in high yields and high purity by the process of the invention.

Intermediates formed in the process of the invention are novel. The invention also provides compounds of the formula VII as racemate in optically enriched or optically pure form,



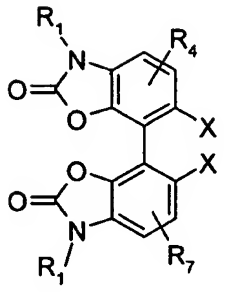
(VII),

where R_1, R_2, R_3, R_4, R_5, R_6, R_7 and X are as defined above, or R_2 is a protective group which can be split off or R_2 and R_3 together form a protective group which can be split off and R_1, R_3, R_4, R_5, R_6, R_7 and X or R_1, R_4, R_5, R_6, R_7 and X are as defined above, and X is chlorine, bromine or iodine.

The preferred embodiments indicated for the compounds of the formulae I and Ia also apply to the compounds of the formulae VII.

Particularly preferred is a compound of the formula VII, where R_1 is methyl, and R_2 and R_3 together form 1, 2-ethylene.

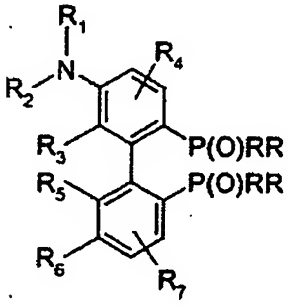
Particularly preferred intermediates also include those of the formula VIIa, as racemate, in optically enriched or optically pure form,



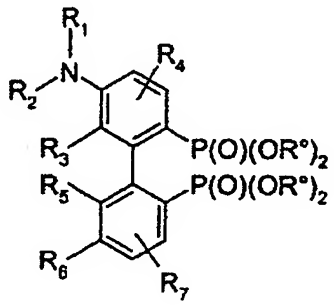
(VIIa),

where X is chlorine, bromine or iodine and R_1, R_4 and R_7 have the meanings indicated for compounds of the formulae I and Ia, including the preferences.

The invention further provides the preproducts of the formula IX in the form of racemates,

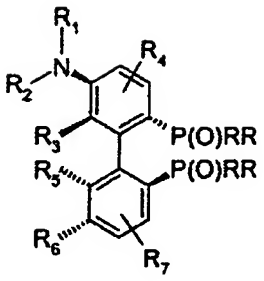


(IX)

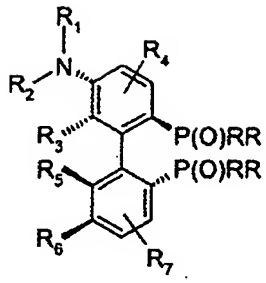


(IXa),

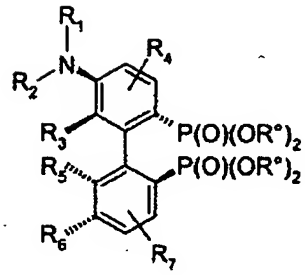
and the enantiomers of the formulae X, Xa, Xb and Xc,



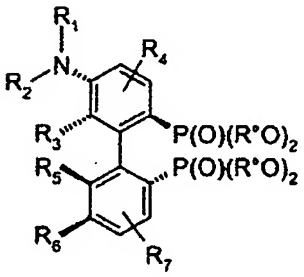
(X)



(Xa),



(Xb)

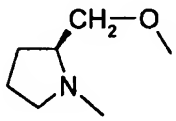


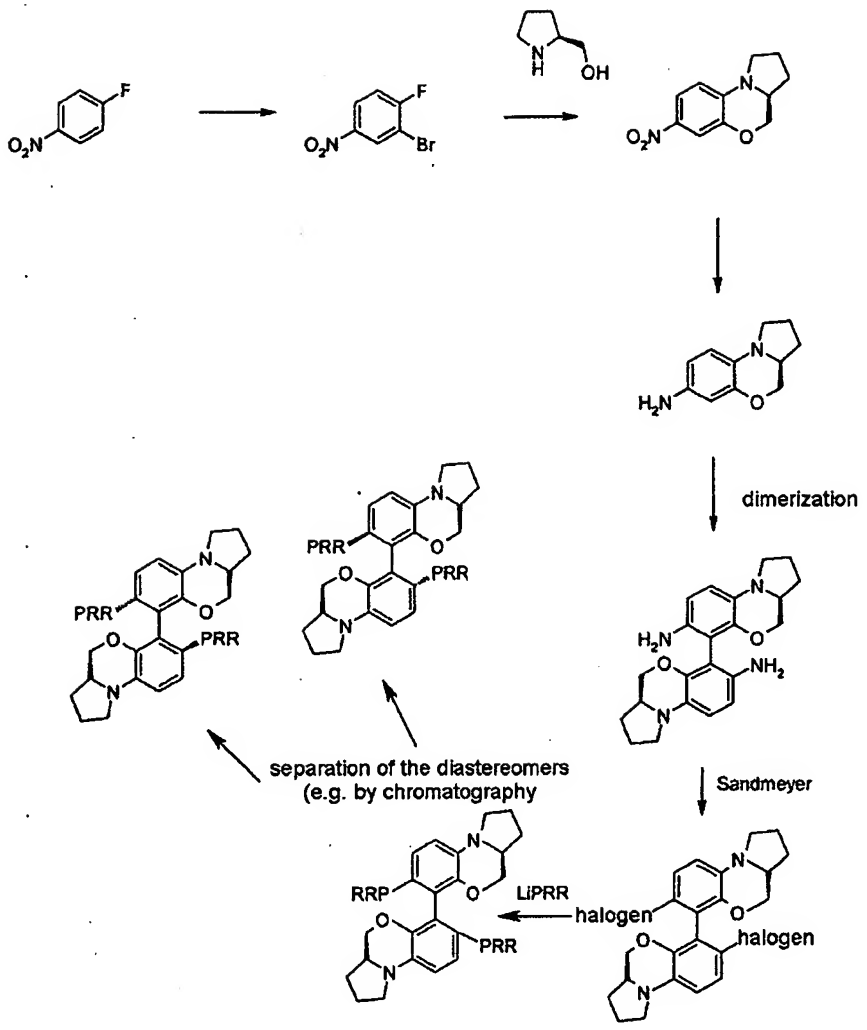
(Xc),

where R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R have the meanings indicated for the compounds of the formulae I and Ia, including the preferences. And R° is C_1-C_6-alkyl or phenyl.

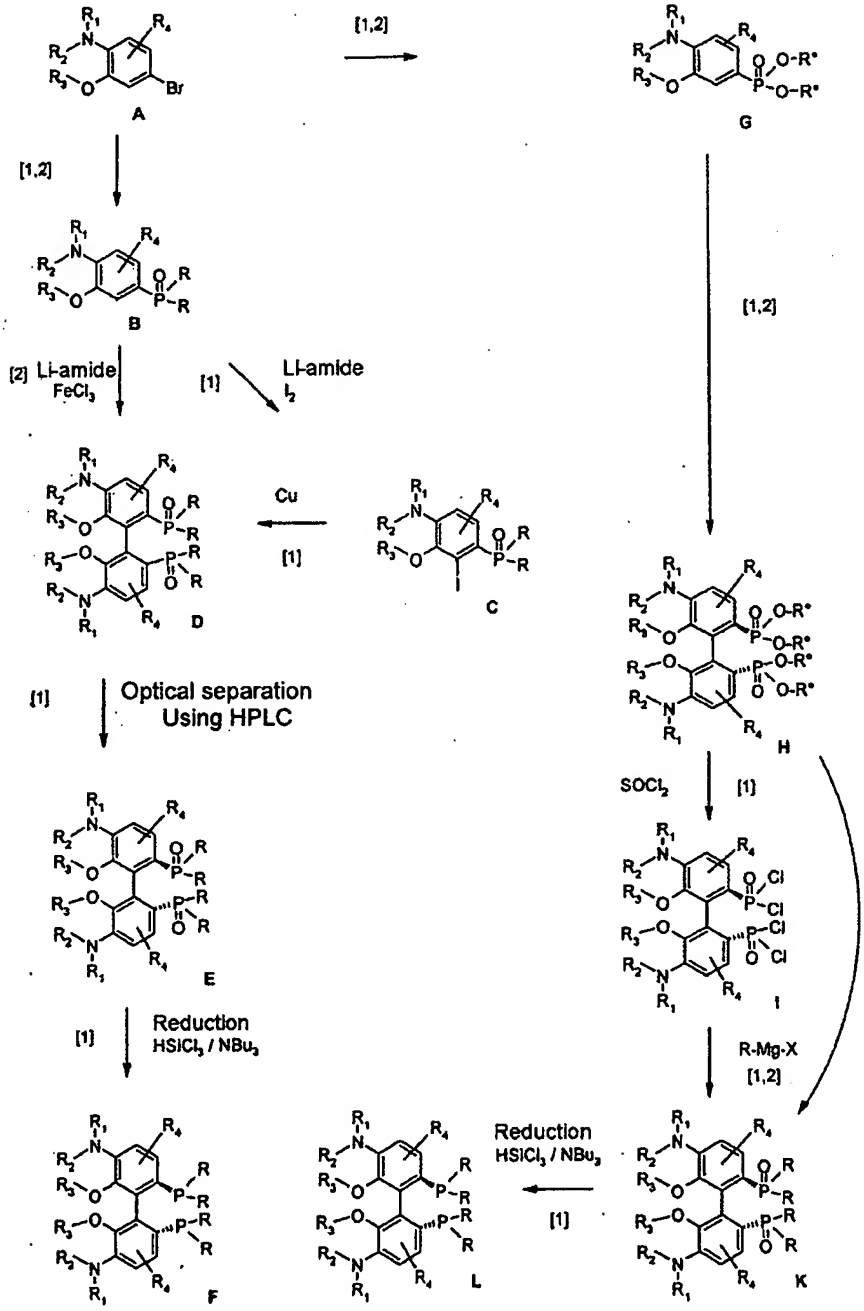
Particular preference is given to compounds of the formulae IX, IXa, X, Xa, Xb and Xc, in which R_1 is methyl, R_2 and R_3 together are 1,2-ethylene and R_4, R_5, R_6, R_7 and R have the meanings indicated for compounds of the formulae I and Ia, including the preferences, and R° is C_1-C_6-alkyl or phenyl.

Possible methods of preparation are shown below for illustrative purposes as reaction schemes. Compounds of the formulae I and Ia, in which R_1R_2N and R_3O together are the group of the formula



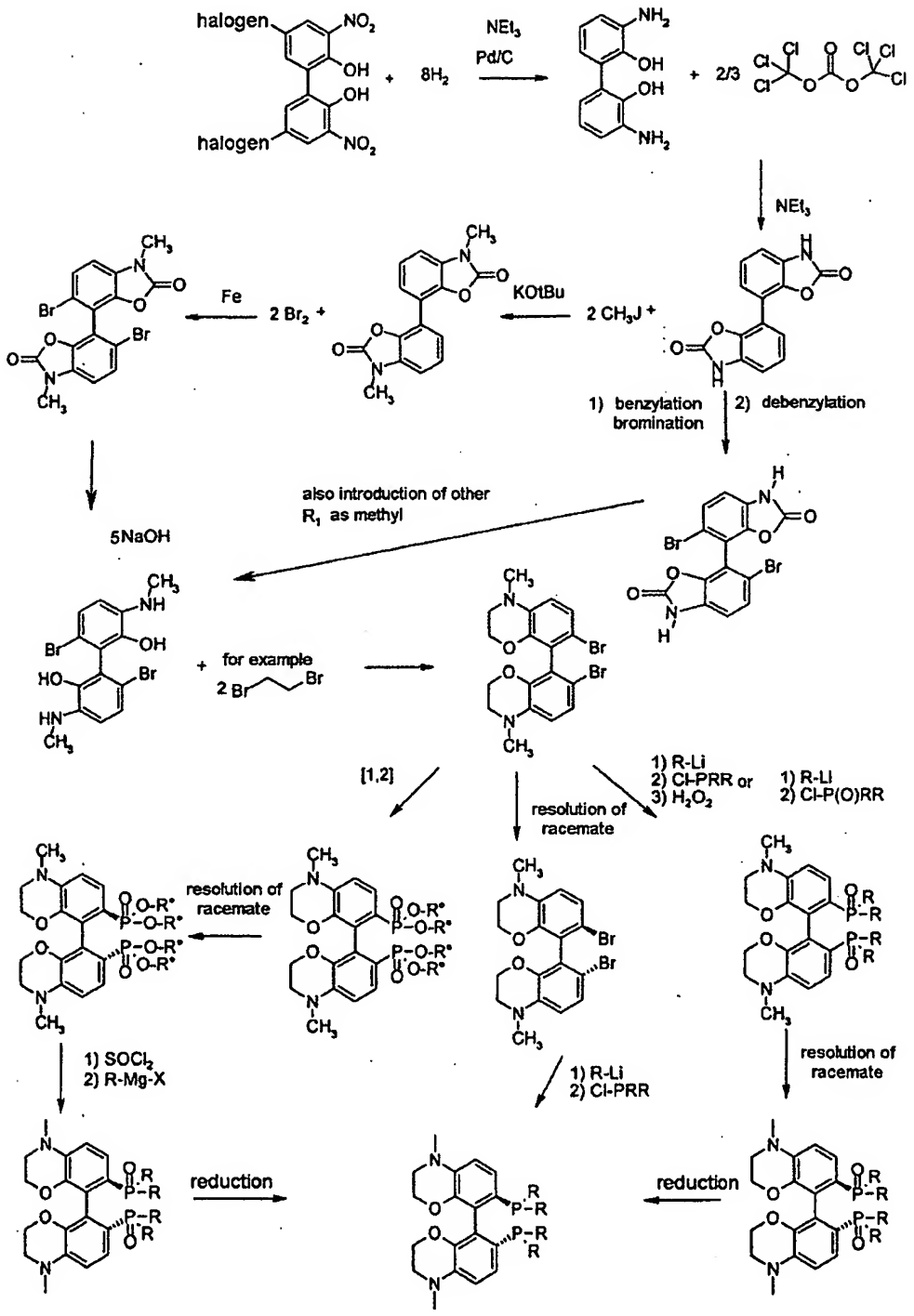

dimerization
separation of the diastereomers
(e.g. by chromatography
Sandmeyer
LiPRR
halogen
halogen
PRR
RRP

Preparation of symmetrical compounds (route 1 via coupling):

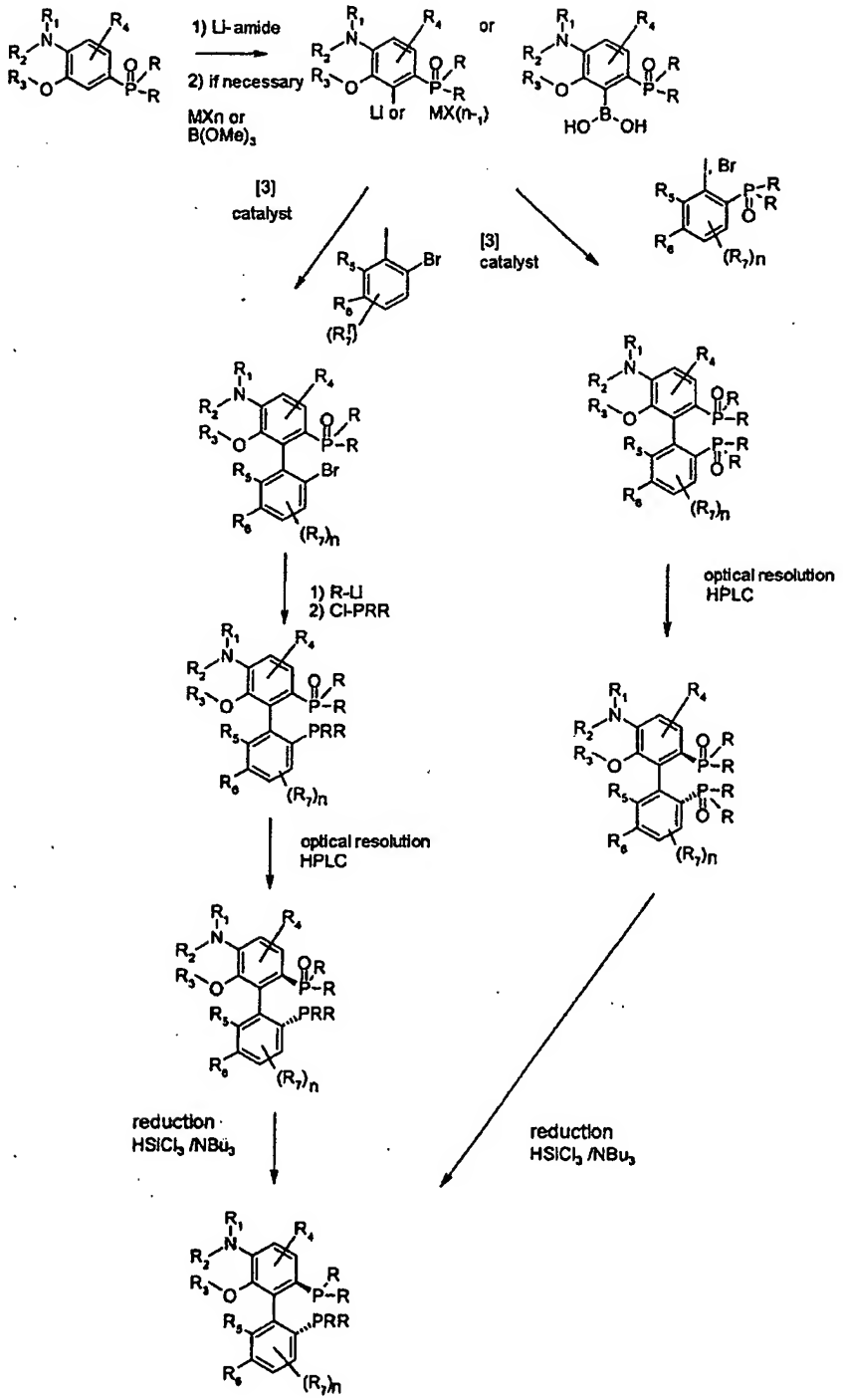


Rg can be, for example, C_1-C_4-alkyl or phenyl.

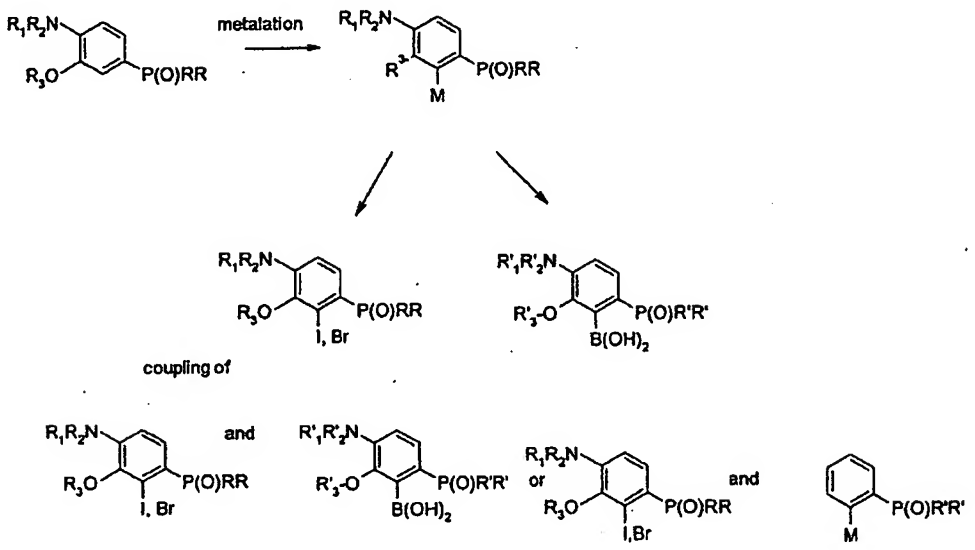
Route 2, via preformed biaryl:



Preparation of unsymmetrical compounds:



Unsymmetrically substituted compounds can also be obtained according to the following scheme:



The novel compounds of the formula I are ligands for complexes of metals selected from the group of the TM8 metals, in particular from the group consisting of Ru, Rh and Ir, which are excellent catalysts or catalyst precursors for asymmetric syntheses, for example the asymmetric hydrogenation of prochiral, unsaturated, organic compounds. If prochiral unsaturated organic compounds are used, a very high excess of optical isomers can be induced in the synthesis of organic compounds and a high chemical conversion can be achieved in short reaction times. Enantioselectivity is considerably higher in selected substrates (e.g. 2-methylcinnamic acid) in comparision with known ditertiany ferrocenyl diphosphines.

The invention further provides complexes of metals selected from the group of the TM8 metals with compounds of the formulae I and Ia as ligands.

Possible metals are, for example, Cu, Ag, Au, Ni, Co, Rh, Pd, Ir, Ru and Pt. Preferred metals are rhodium and iridium and also ruthenium, platinum and palladium.

Particularly preferred metals are ruthenium, rhodium and iridium.

The metal complexes can, depending on the oxidation number and coordination number of the metal atom, contain further ligands and/or anions. They can also be cationic metal complexes. Analogous metal complexes of this type and their preparation are widely described in the literature.

The metal complexes can, for example, correspond to the general formulae XI and XII,

A_1MeL_n (XI), $(A_1MeL_n)^{(z+)}(E^-)_z$ (XII),

where A_1 is a compound of the formula I or Ia,
L represents identical or different monodentate, anionic or nonionic ligands, or two L form identical or different bidentate, anionic or nonionic ligands;
n is 2, 3 or 4 when L is a monodentate ligand or n is 1 or 2 when L is a bidentate ligand;
z is 1, 2 or 3;
Me is a metal selected from the group consisting of Rh and Ir; with the metal having the oxidation state 0, 1, 2, 3 or 4;
E^- is the anion of an oxo acid or complex acid; and
the anionic ligands balance the charge of the oxidation stage 1, 2, 3 or 4 of the metal.

The above-described preferences and embodiments apply to the compounds of the formula XI and XII.

Monodentate nonionic ligands can, for example, be selected from the group consisting of olefins (for example ethylene, propylene), allyls (allyl, 2-methallyl), solvating solvents (nitriles, linear or cyclic ethers, unalkylated or N-alkylated amides and lactams, amines, phosphines, alcohols, carboxylic esters, sulfonic esters), nitrogen monoxide and carbon monoxide.

Monodentate anionic ligands can, for example, be selected from the group consisting of halide (F, Cl, Br, I), pseudohalide (cyanide, cyanate, isocyanate) and anions of carboxylic acids, sulfonic acids and phosphonic acids (carbonate, formate, acetate, propionate, methylsulfonate, trifluoromethylsulfonate, phenylsulfonate, tosylate).

Bidentate nonionic ligands can, for example, be selected from the group consisting of linear or cyclic diolefins (for example hexadiene, cyclooctadiene, norbornadiene), dinitriles

(malononitrile), unalkylated or N-alkylated diamides of carboxylic acids, diamines, diphosphines, diols, acetonylacetonates, dicarboxylic diesters and disulfonic diesters.

Bidentate anionic ligands can, for example, be selected from the group consisting of the anions of dicarboxylic acids, disulfonic acids and diphosphonic acids (for example of oxalic acid, malonic acid, succinic acid, maleic acid, methylenedisulfonic acid and methylenediphosphonic acid).

Preferred metal complexes also include ones in which E is $-Cl^-$, $-Br^-$, $-I^-$, ClO_4^-, $CF_3SO_3^-$, $CH_3SO_3^-$, HSO_4^-, BF_4^-, $B(phenyl)_4^-$, $B(C_6F_5)_4^-$, B(3,5-bistrifluoromethylphenyl)$_4^-$, PF_6^-, $SbCl_6^-$, AsF_6^- or SbF_6^-.

Very particularly preferred metal complexes, which are particularly suitable for hydrogenations, correspond to the formulae XIII and XIV,

$[A_1Me_1YZ]$ (XIII), $[A_1Me_1Y]^+E_1^-$ (XIV),

where
A_1 is a compound of the formula I or Ia;
Me_1 is rhodium or iridium;
Y represents two olefins or one diene;
Z is Cl, Br or I; and
E_1^- is the anion of an oxo acid or complex acid.

The above-described embodiments and preferences apply to the compounds of the formulae I and Ia.

Olefins as Y can be C_2-C_{12}-, preferably C_2-C_6- and particularly preferably C_2-C_4-olefins. Examples are propene, 1-butene and in particular ethylene. The diene can contain from 5 to 12, preferably from 5 to 8, carbon atoms and can be an open-chain, cyclic or polycyclic diene. The two olefin groups of the diene are preferably connected by one or two CH_2 groups. Examples are 1,3-pentadiene, cyclopentadiene, 1,5-hexadiene, 1,4-cyclohexadiene, 1,4- or 1,5-heptadiene, 1,4- or 1,5-cycloheptadiene, 1,4- or 1,5-octadiene, 1,4- or 1,5-cyclooctadiene and norbornadiene. Y preferably represents two ethylene molecules or 1,5-hexadiene, 1,5-cyclooctadiene or norbornadiene.

In the formula XVI, Z is preferably Cl or Br. Examples of E_1 are ClO_4^-, $CF_3SO_3^-$, $CH_3SO_3^-$, HSO_4^-, BF_4^-, $B(phenyl)_4^-$, PF_6^-, $SbCl_6^-$, AsF_6^- or SbF_6^-.

Ruthenium complexes according to the invention can, for example, correspond to the formula XV,

$$[Ru_aH_bZ_c(A_1)_dL_e]_f(E^k)_g(S)_h \qquad (XV),$$

where
Z is Cl, Br or I; A_1 is a compound of the formula I or Ia; L represents identical or different ligands; E^- is the anion of an oxo acid, mineral acid or complex acid; S is a solvent capable of coordination as ligand; and a is from 1 to 3, b is from 0 to 4, c is from 0 to 6, d is from 1 to 3, e is from 0 to 4, f is from 1 to 3, g is from 1 to 4, h is from 0 to 6 and k is from 1 to 4, with the total charge of the complex being zero.

The abovementioned preferences for Z, A_1, L and E^- apply to the compounds of the formula XV. The ligands L can additionally be arenes or heteroarenes (for example benzene, naphthalene, methylbenzene, xylene, cumene, 1,3,5-mesitylene, pyridine, biphenyl, pyrrole, benzimidazole or cyclopentadienyl) and metal salts which act as Lewis acids (for example $ZnCl_2$, $AlCl_3$, $TiCl_4$ and $SnCl_4$). The solvent ligands can be, for example, alcohols, amines, acid amides, lactams and sulfones.

Complexes of this type are described in the references mentioned below and the references cited therein:
D. J. Ager, S. A. Laneman, Tetrahedron: Asymmetry, **8**, *1997*, 3327 – 3355;
T. Ohkuma, R. Noyori in Comprehensive Asymmetric Catalysis (E.N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.), Springer, Berlin, 1999, 199-246;
J. M. Brown in Comprehensive Asymmetric Catalysis (E.N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.), Springer, Berlin, 1999, 122 – 182;
T. Ohkuma, M. Kitamura, R. Noyori in Catalytic Asymmetric Synthesis, 2nd Edition (I. Ojima, Ed.), Wiley-VCH New York, 2000, 1 – 110;
N. Zanetti, et al. Organometallics **15**, 1996, 860.

More specific ruthenium complexes having corresponding formulae but different diphosphine ligands are described in the following references:

$[Ru_aH_bCl_c(A_1)_darene_e]$ $(amine)_h$: EP-A1-0 269 395 and EP-A1-0174 057;
$[Ru_a(A_1)]E^-$, more specifically $[Ru(A_1)]$ E^- and $[RuH((A_1)]E^-$: EP-A1-0 256 634;
$[Ru(A_1)(carboxylate)_2]$: US-A-4 739 084 and AP-A1-0 245 959;
$[Ru(A_1)_2(Lewis\ acid)](NC_2H_5)_3$, $[Ru(A_1)_2(Lewis\ acid)](acetate)$: EP-A1-0 307 168;
$[RuZ(arene)(A_1)]halide$, $[Ru(Z)(arene)(A_1)]E^-$: EP-A1-0 366 390;
$[RuZ_2(A_1)(chiral\ amine)]$: H. Doucet et al., Angew. Chem. Int. Ed. **37**, 1998, 1703; T. Ohkuma, et al., J. Am. Chem. Soc., **120**, 1998 13529; T. Ohkuma, et al., J. Am. Chem. Soc., **122**, 2000, 6510.
$[RuZ_2(A_1)(pyridine)_2]$: O. M. Akotsi et al., Chirality, 12 (2000) 514.

Some specific and preferred ruthenium complexes are: $[Ru(acetate)_2(A_1)]$, $[Ru(OOCCF_3)_2(A_1)]$, $[RuCl_2(A_1)]$, $[RuBr_2(A_1)]$, $[RuI_2(A_1)]$, $[Ru_2Cl_4(A_1)_2](Nethyl_3)$, $[Ru_2Cl_4(A_1)_2]$-$(Nethyl_3)(xylene)$, $[RuCl(benzene)(A_1)]Cl$, $[RuBr(benzene)(A_1)]Br$, $[RuI(benzene)(A_1)]I$, $[RuCl(p\text{-}cumene)(A_1)]Cl$, $[RuBr(p\text{-}cumene)(A_1)]Br$, $[RuI(p\text{-}cumene)(A_1)]I$, $[Ru(2\text{-}methallyl)_2(A_1)]$, $[RuCl_2(phenylCN)_2(A_1)]$, $[Ru(A_1)(AcO)_2(ethanol)_2]$, $[(Cp)Ru(A_1)]Cl$, $[(Cp)Ru(A_1)]PF_6$, $[RuCl(Pphenyl_3)(A_1)]_2(\eta\text{-}Cl)_2$, $[RuCl_2(A_1)(dpen)]$ and $[RuCl_2(A_1)(daipen)]$. Cp is cyclopentadienyl. dpen and daipen are chiral ethylenediamines, for example 1,2-diphenylethylene-1,2-diamine or 1,1-di(p-methoxyphenyl)2-isopropylethylene-1,2-diamine.

The metal complexes of the invention are prepared by methods known from the literature (cf. US-A-5,371,256, US-A-5,446,844, US-A-5,583,241, and E. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis I to III, Springer Verlag, Berlin, 1999, and references cited therein).

The metal complexes of the invention are homogeneous catalysts, or catalyst precursors which can be activated under the reaction conditions, which can be used for asymmetric addition reactions onto prochiral, unsaturated, organic compounds.

The metal complexes can, for example, be used for the asymmetric hydrogenation (addition of hydrogen) of prochiral compounds having carbon-carbon or carbon-heteroatom double bonds. Such hydrogenations using soluble homogeneous metal complexes are described, for example, in Pure and Appl. Chem., Vol. 68, No. 1, pp. 131-138 (1996). Preferred

unsaturated compounds to be hydrogenated contain the groups C=C, C=N and/or C=O. According to the invention, metal complexes of ruthenium, rhodium and iridium are preferably used for the hydrogenation.

The metal complexes of the invention can also be used as catalysts for the asymmetric hydroboration (addition of boron hydrides) of prochiral organic compounds having carbon-carbon double bonds. Such hydroborations are described, for example, by Tamio Hayashi in E. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis I to III, Springer Verlag, Berlin, 1999, pages 351 to 364. Suitable boron hydrides are, for example, catecholboranes. The chiral boron compounds can be used in syntheses and/or be converted in a manner known per se into other chiral organic compounds which are valuable buiding blocks for the preparation of chiral intermediates or active substances. An example of such a reaction is the preparation of 3-hydroxytetrahydrofuran (as described in DE 19,807,330).

The metal complexes of the invention can also be used as catalysts for the asymmetric hydrosilylation (addition of silanes) of prochiral organic compounds having carbon-carbon or carbon-heteroatom double bonds. Such hydrosilylations are described, for example, by G. Pioda and A. Togni in Tetrahedron: Asymmetry, 1998, 9, 3093 or by S. Uemura, et al. in Chem. Commun. 1996, 847. Suitable silanes are, for example, trichlorosilane or diphenylsilane. The hydrosilylation of, for example, C=O- and C=N- groups is preferably carried out using metal complexes of rhodium and iridium. The hydrosilylation of, for example, C=C groups is preferably carried out using metal complexes of palladium. The chiral silyl compounds can be used in syntheses and/or be converted in a manner known per se into other chiral organic compounds which are valuable building blocks for the preparation of chiral intermediates or active substances. Examples of such reactions are hydrolyses to form alcohols.

The metal complexes of the invention can also be used as catalysts for asymmetric allylic substitution reactions (addition of carbon nucleophiles onto allyl compounds. Such allylations are described, for example, by A. Pfaltz and M. Lautens in E. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis I to III, Springer Verlag, Berlin, 1999, pages 833 to 884. Suitable precursors for allyl compounds are, for example, 1,3-diphenyl-3-acetoxy-1-propene or 3-acetoxy-1-cyclohexene. Metal complexes of palladium are preferably used for this reaction. The chiral allyl compounds can be used in syntheses for preparing chiral intermediates or active substances.

The metal complexes of the invention can also be used as catalysts for the asymmetric amination (addition of amines onto allyl compounds) or etherification (addition of alcohols or phenols onto allyl compounds). Such aminations and etherifications are described, for example, by A. Pfaltz and M. Lautens in E. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis I to III, Springer Verlag, Berlin, 1999, pages 833 to 884. Suitable amines include ammonia and primary and secondary amines. Suitable alcohols are phenols and aliphatic alcohols. Metal complexes of palladium are preferably used for the amination or etherification of the allyl compounds. The chiral amines and ethers can be used in syntheses for preparing chiral intermediates or active substances.

The metal complexes of the invention can also be used as catalysts for asymmetric isomerization, cf. M. Beller et al. in Transition Metals for Organic Synthesis, Volume 1, Wiley-VCH, Weinheim 1998, pages 147-156.

The invention further provides for the use of the metal complexes of the invention as homogeneous catalysts for preparing chiral organic compounds by asymmetric addition of hydrogen, boron hydrides or silanes onto a carbon-carbon or carbon-heteroatom multiple bond in prochiral organic compounds, or the asymmetric addition of carbon nucleophiles or amines onto allyl compounds.

A further aspect of the invention is a process for preparing chiral organic compounds by assymetric addition of hydrogen, boron hydrides or silanes onto a carbon-carbon or carbon-heteroatom multiple bond in prochiral organic compounds, or the asymmetric addition of carbon nucleophiles, alcohols or amines onto allyl compounds in the presence of a catalyst, which is characterized in that the addition reaction is carried out in the presence of catalytic amounts of at least one metal complex according to the invention.

Preferred prochiral, unsaturated compounds to be hydrogenated can contain one or more, identical or different C=C, C=N and/or C=O groups in open-chain or cyclic organic compounds, with the C=C, C=N and/or C=O groups being able to be part of a ring system or being exocyclic groups. The prochiral unsaturated compounds can be alkenes, cycloalkenes, heteroalkenes and also open-chain or cyclic ketones, ketimines and kethydrazones. They can, for example, correspond to the formula XVI,

$$R_{15}R_{16}C=D \qquad \text{(XVI)},$$

where R_{15} and R_{16} are selected so that the compound is prochiral and are each, independently of one another, an open-chain or cyclic hydrocarbon radical or heterohydrocarbon radical containing heteroatoms selected from the group consisting of O, S and N and each have from 1 to 30, preferably from 1 to 20, carbon atoms;
D is O or a radical of the formula $CR_{17}R_{18}$ or NR_{19};
R_{17} and R_{18} are each, independently of one another, defined as for R_{15} and R_{16},
R_{19} is hydrogen, C_1-C_{12}-alkyl, C_1-C_{12}-alkoxy, C_3-C_{12}-cycloalkyl, C_3-C_{12}-cycloalkyl-C_1-C_6-alkyl, C_3-C_{11}-heterocycloalkyl, C_3-C_{11}-heterocycloalkyl-C_1-C_6-alkyl, C_6-C_{14}-aryl, C_5-C_{13}-heteroaryl, C_7-C_{16}-aralkyl or C_6-C_{14}-heteroaralkyl,
R_{15} and R_{16} together with the carbon atom to which they are bound form a hydrocarbon ring or heterohydrocarbon ring having from 3 to 12 ring atoms;
R_{15} and R_{17} together with the C=C group to which they are bound form a hydrocarbon ring or heterohydrocarbon ring having from 3 to 12 ring atoms;
R_{15} and R_{19} together with the C=N group to which they are bound form a hydrocarbon ring or heterohydrocarbon ring having from 3 to 12 ring atoms;
the heteroatoms in the heterocyclic rings are selected from the group consisting of O, S and N;
and R_{15}, R_{16}, R_{17}, R_{18} and R_{19} are unsubstituted or substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy, cyclohexyl, C_6-C_{10}-aryl, C_7-C_{12}-aralkyl, C_1-C_4-alkyl-C_6-C_{10}-aryl, C_1-C_4-alkoxy-C_6-C_{10}-aryl, C_1-C_4-alkyl-C_7-C_{12}-aralkyl, C_1-C_4-alkoxy-C_7-C_{12}-aralkyl, -OH, =O, $-NR_{21}R_{122}$, $-CO-OR_{20}$ or $-CO-NR_{21}R_{22}$, where R_{20} is H, an alkali metal, C_1-C_6-alkyl, cyclohexyl, phenyl or benzyl and R_{21} and R_{22} are each, independently of one another, hydrogen, C_1-C_6-alkyl, cyclohexyl, phenyl or benzyl, or R_{21} and R_{22} together are tetramethylene, pentamethylene or 3-oxapentylene.

Examples and preferences for substituents have been mentioned above.

R_{15} and R_{16} can be, for example, C_1-C_{20}-alkyl and preferably C_1-C_{12}-alkyl, C_1-C_{20}-heteroalkyl and preferably C_1-C_{12}-heteroalkyl containing heteroatoms selected from the group consisting of O, S and N, C_3-C_{12}-cycloalkyl and preferably C_4-C_8-cycloalkyl, C-bonded C_3-C_{11}-heterocycloalkyl and preferably C_4-C_8-heterocycloalkyl containing heteroatoms selected from the group consisting of O, S and N, C_3-C_{12}-cycloalkyl-C_1-C_6-alkyl and preferably C_4-C_8-cycloalkyl-C_1-C_6-alkyl, C_3-C_{11}-heterocycloalkyl-C_1-C_6-alkyl and preferably C_4-C_8-heterocycloalkyl-C_1-C_6-alkyl containing heteroatoms selected from the group consisting of O, S and N, C_6-C_{14}-aryl and preferably C_6-C_{10}-Aryl, C_5-C_{13}-heteroaryl and preferably

C_5-C_9-heteroaryl containing heteroatoms selected from the group consisting of O, S and N, C_7-C_{15}-aralkyl and preferably C_7-C_{11}-aralkyl, C_6-C_{12}-heteroaralkyl and preferably C_6-C_{10}-heteroaralkyl containing heteroatoms selected from the group consisting of O, S and N.

If R_{15} and R_{16}, R_{15} and R_{17}, or R_{15} and R_{19} together with the group to which they are bound form a hydrocarbon ring or heterohydrocarbon ring, the ring preferably contains from 4 to 8 ring atoms. The heterohydrocarbon ring can contain, for example, from 1 to 3, preferably one or two, heteroatoms.

R_{19} is preferably hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_4-C_8-cycloalkyl, C_4-C_8-cycloalkyl-C_1-C_4-alkyl, C_4-C_{10}-heterocycloalkyl, C_4-C_{10}-heterocycloalkyl-C_1-C_4-alkyl, C_6-C_{10}-aryl, C_5-C_9-heteroaryl, C_7-C_{12}-aralkyl and C_5-C_{13}-heteroaralkyl.

Some examples of unsaturated organic compounds are acetophenone, 4-methoxy-acetophenone, 4-trifluoromethylacetophenone, 4-nitroacetophenone, 2-chloroacetophenone, corresponding unsubstituted or N-substituted acetophenone benzylimines, unsubstituted or substituted benzocyclohexanone or benzocyclopentanone and corresponding imines, imines from the group consisting of unsubstituted or substituted tetrahydroquinoline, tetrahydropyridine and dihydropyrrole, and unsaturated carboxylic acids, carboxylic esters, carboxamides and carboxylic acid salts, for example α- and, if appropriate, β-substituted acrylic acids or crotonic acids. Preferred carboxylic acids are carboxylic acids of the formula

$$R_{23}\text{-}CH=C(R_{24})\text{-}C(O)OH$$

and also their salts, esters and amides, where R_{23} is C_1-C_6-alkyl, unsubstituted C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl substituted by from 1 to 4 C_1-C_6-alkyl, C_1-C_6-alkoxy or C_1-C_6-alkoxy-C_1-C_4-alkoxy groups or unsubstituted C_6-C_{10}-aryl or C_6-C_{10}-aryl substituted by from 1 to 4 C_1-C_6-alkyl, C_1-C_6-alkoxy or C_1-C_6-alkoxy-C_1-C_4-alkoxy groups, preferably phenyl, and R_{24} is linear or branched C_1-C_6-alkyl (for example isopropyl), unsubstituted cyclopentyl, cyclohexyl or phenyl or cyclopentyl, cyclohexyl or phenyl substituted as defined above or protected amino (for example acetylamino).

Further suitable substrates for the hydrogenation are, for example, prochiral allyl alcohols and β-enamides. Particularly suitable substrates for the hydrogenation using ruthenium

1,3-diketones and prochiral ketones, α– and β-alkoxyketones and α– and β-hydroxyketones, α– and β-haloketones and α– and β-aminoketones.

The process of the invention can be carried out at low or elevated temperatures, for example temperatures of from -20 to 150°C, preferably from -10 to 100 °C, and particularly preferably from 10 to 80°C. The optical yields are generally better at relatively low temperature than at higher temperatures.

The process of the invention can be carried out at atmospheric pressure or under superatmospheric pressure. The pressure can be, for example, from 10^5 to $2x10^7$ Pa (pascal). Hydrogenations are preferably carried out at superatmospheric pressure.

Catalysts are preferably used in amounts of from 0.00001 to 10 mol%, particularly preferably from 0.0001 to 10 mol%, and very particularly preferably from 0.001 to 5 mol%, based on the compound to be hydrogenated.

The preparation of the catalysts and also the hydrogenations and addition reactions can be carried out without solvent or in the presence of an inert solvent, with it being possible to use one solvent or mixtures of solvents. Suitable solvents have been mentioned above.

The reactions can be carried out in the presence of cocatalysts, for example quaternary ammonium halides (tetrabutylammonium iodide) and/or in the presence of protic acids, for example mineral acids (cf. for example, US-A-5,371,256, US-A-5,446,844 and US-A-5,583,241 and EP-A-0 691 949). The cocatalysts are particularly useful for hydrogenations.

The metal complexes used as catalysts can be added as separately prepared isolated compounds or can be formed in situ prior to the reaction and then be mixed with the substrate to be hydrogenated. It can be advantageous to add additional ligands in the reaction using isolated metal complexes or to use an excess of ligands in the in-situ preparation. The excess can be, for example, from 1 to 10 mol, preferably from 1 to 5 mol, based on the metal compound used for the preparation. In the case of the in situ preparation of the catalysts, it is also possible to use salts of the diphosphine ligands, for example halides or tetrafluoroborates.

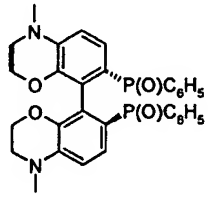
The process of the invention is generally carried out by firstly placing the catalyst in a reaction vessel and then adding the substrate, if desired reaction auxiliaries and the compound to be added on, and then starting the reaction. Gaseous compounds to be added on, for example hydrogen or ammonia, are preferably injected under pressure. The process can be carried out continuously or batchwise in various types of reactor.

The chiral organic compounds which can be prepared according to the invention are active substances or intermediates for the preparation of such substances, in particular in the field of preparation of pharmaceuticals and agrochemicals. Thus, for example, o,o-dialkylaryl-ketamine derivatives, in particular those bearing alkyl and/or alkoxyalkyl groups, act as fungicides, in particular as herbicides. The derivatives can be amine salts, acid amides, e.g. of chloroacetic acid, tertiary amines and ammonium salts (cf., for example, EP-A-0 077 755 and EP-A-0 115 470).

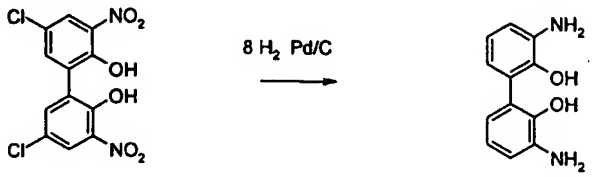
The following examples illustrate the invention.

A) Preparation of intermediates

Example A1: Preparation of compounds of the formula:



a) Preparation of 2,2'-dihydroxy-3,3'-diaminobiphenyl (2):

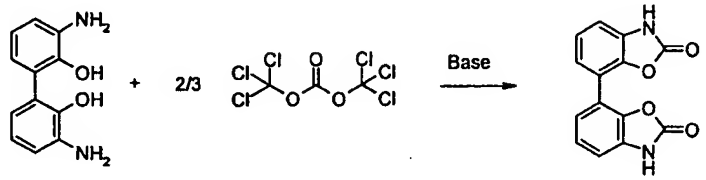


(1) (2)

10 g of niclofolan (1) are dissolved in 100 ml of tetrahydrofuran (THF) and 17.6 g of triethylamine. After addition of 4 g of palladium on carbon 5% and a further 4 g after 40 hours, hydrogenation is carried out to saturation over a total period of about 88 hours. The solution is filtered through Hyflo and is immediately processed further without

evaporation. Assumed yield of (2): 100%. R_f 0.11 (CH_2Cl_2/methanol/NH_4OH 25% (60:10:1)). ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 6.68 (2 H, m), 6.48 (4 H, m).

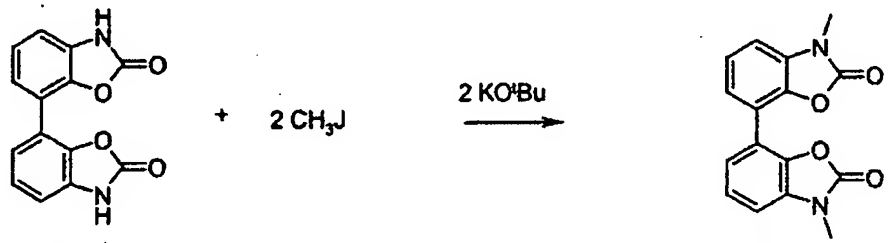
b) Preparation of compound (3):



(2) (3)

The filtered solution from the hydrogenation comprising (2), which already contains sufficient triethylamine, is cooled in ice and a solution of 5.67 g of triphosgene in 10ml of THF is quickly added dropwise. The mixture is firstly stirred at 0°C for 30 minutes and subsequently at room temperature (RT) for 1 hour. The product is precipitated by means of water, acidified with 4N HCl and then filtered off. The dried crystals are digested with methanol and filtered off with suction. This gives 4.9 g of brown crystals of the compound (3) (64% of theory), melting point: >270°C; R_f 0.45 (CH_2Cl_2/MeOH/NH_4OH 25% (60:10:1)). ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.85 (2 H, s), 7.35 (2 H, d), 7.29 (2 H, t), 7.15 (2 H, d).

c) Preparation of compound (4):



3 4

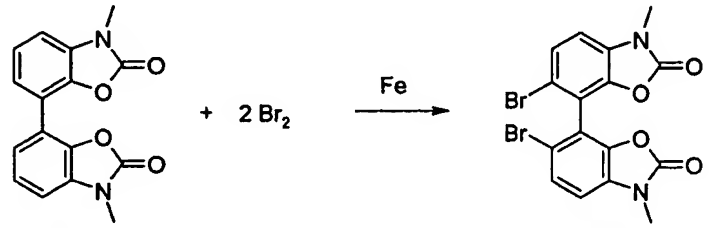
35 g of the carbamate (3) are dissolved in 700 ml of dimethylformamide (DMF) and 32.2 g of potassium tert-butoxide are added a little at a time at 15 – 20°C (ice bath). After stirring for one hour at RT, 17.9 ml of methyl iodide are added at 8°C. This results in the temperature rising to 12°C. The mixture is stirred at RT for 2 days and another 0.1 equivalent of base and 0.1 equivalent of methyl iodide are then added. After stirring at RT for 1 hour and then briefly heating to 50°C, the suspension is evaporated. The residue is stirred with about

500 ml of water and filtered off with suction. This gives 37.07 g of the compound (4) in the form of a fine brown powder (96% of theory).

Melting point >270°C; R_f 0.60 (toluene/ethyl acetate/CH_2Cl_2/formic acid (24:40:40:4)).

^{1}H-NMR (300 MHz, ($CDCl_3$): 7.59 (2 H, d), 7.40 (2 H, t) 7.0 (2 H, d), 3.45 (6H, s).

d) Preparation of compound (5):



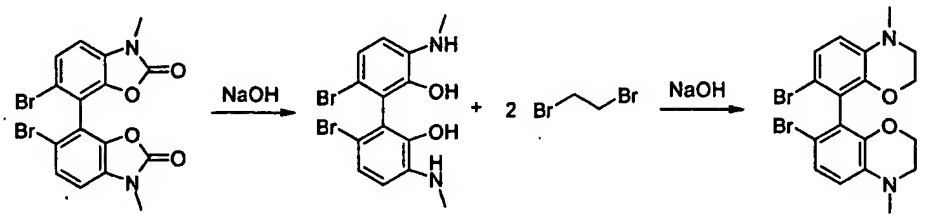
(4) (5)

37 g of the methylated carbamate (4) are dissolved in 260 ml of nitrobenzene at 200°C. After addition of 250 mg of iron powder, 14 ml of bromine are dissolved in a little nitrobenzene, added dropwise at 150-180°C over a period of 25 minutes and the mixture is stirred at 160°C-100°C for 2 hours. A further 5 ml of bromine are then added and the mixture is stirred at 80°C for another 1 hour. After cooling to RT, which results in the product beginning to precipitate, the crude product is isolated virtually quantitatively by addition of 300 ml of petroleum ether and 300 ml of diethyl ether and subsequent filtration. The crude product is briefly heated with 150 ml of acetonitrile and then filtered off with suction at RT. Drying in a high vacuum/80°C gives 37.1 g (65% of theory) of the isomerically pure product (5) as brown fine crystals.

Melting point >270°C; R_f 0.65 (toluene/ethyl acetate/CH_2Cl_2/formic acid (24:40:40:4)).

^{1}H-NMR (300 MHz, ($CDCl_3$): 7.56 (2 H, d), 6.95 (2 H, d), 3.43 (6 H, s).

e) Preparation of compound (7):



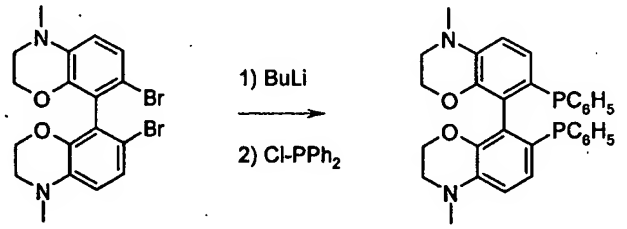
(5) (6) (7)

38 g of the dibromocarbamate (5) are dissolved together with 400 mg of BHT in 590 ml of dimethyl sulfoxide (DMSO) at 95°C and the mixture is stirred at this temperature together with 200 ml of 2N aqueous sodium hydroxide solution under argon/with exclusion of light for 15-30 minutes (HPLC monitoring). The aminophenol intermediate (6) obtained in this way is immediately processed further: firstly cooled and at an internal temperature of 7°C admixed with 144 ml of dibromoethane. After 10 minutes, the ice bath is removed and the mixture is stirred at RT for another 21 hours. It is then allowed to react at 95°C for 2 hours. The reaction mixture is diluted with water and then extracted twice with CH_2Cl_2 and washed twice with water. The organic phase is dried over $MgSO_4$ and evaporated to dryness. 56 g of crude product are separated on 500 g of silica gel (40-63 µm) using CH_2Cl_2/petroleum ether (4:1). The substance is then taken up on 60 g of silica gel (CH_2Cl_2). The combined pure fractions (22.5 g) are digested with cold methanol, filtered off with suction and dried at 50°C in a high vacuum for 3 days. This gives 20.9 g of pure, white crystals of the compound (7) (55% of theory).

Melting point 211-213°C; R_f 0.39 [CH_2Cl_2/petroleum ether (30-50 4:1)].

^{1}H-NMR (300 MHz, ($CDCl_3$): 7.12 (2 H, d), 6.58 (2 H, d), 4.23 (4 H, t), 3.38 – 3.28 (4 H, m), 2.95 (6 H, m).

f) Preparation of compound (8):



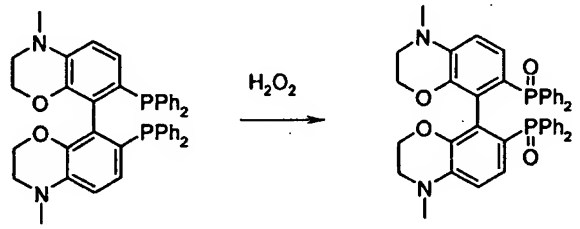
(7) (8)

10 ml n-butylLi (1.6 molar solution in hexane) are slowly added dropwise to a mixture of 3 g of the dibromo compound (7) and 1.8 ml of tetramethylethylenediamine (TMEDA) in 50 ml of toluene at 0-5°C while stirring. The mixture is stirred at this temperature for 30 minutes. The mixture is subsequently cooled to –60°C and 4.2 ml of chlorodiphenylphosphine are added dropwise over a period of 10 minutes while stirring. After stirring at -60°C for 30 minutes, the reaction mixture is slowly allowed to warm to room temperature in the cooling bath while stirring. The resulting suspension is admixed with methylene chloride and filtered. The

solution is extracted with a saturated aqueous $NaHCO_3$ solution and methylene chloride, the organic phase is dried over sodium sulfate and the solvent is removed on a rotary evaporator. Ethyl acetate is added while stirring until the product precipitates. This is filtered off, washed with methanol/ethyl acetate (5:1) and dried in a high vacuum. The product (8) is obtained as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$): 7.28-6.95 (20 H, m); 6.55 (4 H, m_c); 3.73-3.64 (2 H, ^{2}J=10.5, m); 3.50 (2 H, ddd, ^{3}J=7.5, 3.5); 3.16 (2 H, ddd, ^{2}J=10.5, ^{3}J=7.5, 3.5); 2.81-2.78 (2 H, m); 2.78 (6 H, s).
^{31}P-NMR (121.5 MHz, $CDCl_3$): -14.9

g) Preparation of compounds of the formula (9), Ph is phenyl:

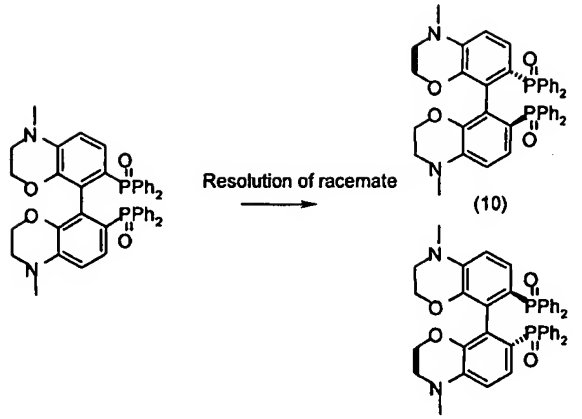


8 9

0.6 ml of hydrogen peroxide (30% in water) is slowly added dropwise to a mixture of 1.8 g of the diphosphine (8) in 25 ml of THF at 0-5°C. The reaction is exothermic. After the addition, the reaction mixture is stirred at 0-5°C for another 10 minutes, and is then allowed to warm slowly to room temperature. After the solvent has been evaporated on a rotary evaporator, the product (9) is obtained as a light-colored solid foam.

^{1}H-NMR (300 MHz, $CDCl_3$): 7.65-7.55 (4 H, m); 7.45-7.21 (12 H, m); 7.21-7.09 (4 H, m); 6.55 (2 H, d_{pd}, ^{3}J=15.0, 7.5); 6.35 (2 H, d_{pd}, ^{3}J=7.5, ^{4}J=3.5); 3.60 (2 H, ddd, ^{2}J=11.3, ^{3}J=3.5); 3.41 (2 H, ddd, ^{2}J=11.25, ^{3}J=7.5, 3.5); 3.13 (2 H, ddd, ^{2}J=11.3, ^{3}J=3.5); 2.85 (2 H, ddd, ^{2}J=11.3, ^{3}J=3.5); 2.77 (6 H, s).
^{31}P-NMR (121.5 MHz, $CDCl_3$): + 30.93.

h) Separation of the enantiomers of the compounds (9):

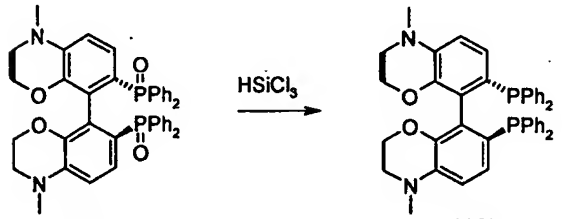


(9) (10) (11)

The resolution of the racemate is carried out by preparative column chromatography (HPLC); column: Chiracell OD 250 x 50 mm, particle size = 10 mm. Hexane/isopropanol (55:45) is used as eluent.

B) Preparation of diphosphine ligands

Example B1: Preparation of the diphosphine ligand (12)



(10) (12)

200 mg of the diphosphine oxide (10), 5 ml of toluene, 1.6 ml of trichlorosilane and 0.43 ml of triethylamine are placed in a steel autoclave, the autoclave is closed and the reaction mixture is stirred at 110°C for 12 hours. After cooling to RT, a little ice is added and the mixture is extracted with a saturated aqueous $NaHCO_3$ solution and methylene chloride. The organic phase is dried over sodium sulfate and the solvent is then removed on a rotary evaporator. The product (12) is purified by flash chromatography (silica gel Merck 60; eluent: toluene containing 2% of triethylamine) and is obtained as a white powder.

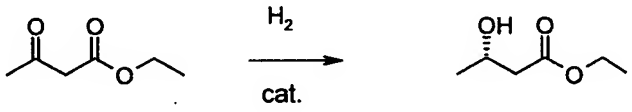
^{1}H-NMR (300 MHz, $CDCl_3$): 7.28-6.95 (20 H, m); 6.55 (4 H, m_c); 3.73-3.64 (2 H, ^{2}J=10.5, m); 3.50 (2 H, ddd, ^{3}J=7.5, 3.5); 3.16 (2 H, ddd, ^{2}J=10.5, ^{3}J=7.5, 3.5); 2.81-2.78 (2 H, m); 2.78 (6 H, s).
^{31}P-NMR (121.5 MHz, $CDCl_3$): -14.9.

C) Preparation of metal complexes

Example C1: Preparation of a ruthenium complex
1.47 mg (0.0015 mmol) of $[RuI_2(p\text{-cumene})]_2$ and 2.14 mg (0.0032 mmol) of diphosphine ligand (12) from Example B1 are introduced into a Schlenk vessel filled with an argon atmosphere. 5 ml of ethanol (degassed) are subsequently added and the solution is stirred at room temperature for 10 minutes. The solution is used directly for the hydrogenation.

D) Use examples

Example D1: Hydrogenation of ethyl 3-ketobutyrate



30 g of ethyl acetoacetate, 5 ml of degassed ethanol and 0.9 ml of 1N HCl are introduced in succession into a Schlenk vessel filled with argon. This solution and the catalyst solution from Example C1 are then transferred in succession by means of a steel capillary into a 50 ml steel autoclave filled with argon. The s/c (substrate/catalyst) ratio is 75 000. The autoclave is closed and a pressure of 50 bar is set using 4 flushing cycles (pressurization with 20 bar of hydrogen). The autoclave is then heated to 80°C, and after 30 minutes the reaction pressure is set to 80 bar. The autoclave is stirred for 19 hours. The heating is subsequently switched off and the autoclave is cooled to room temperature. After depressurization, a reddish reaction solution is isolated. The conversion is >98% (determined by means of GC and ^{1}H-NMR). Removal of the solvent on a rotary evaporator gives a quantitative yield of ethyl (R)-3-hydroxybutyrate having an enantiomeric purity of 97.1% ee. (determined by means of GC after reaction with trifluoroacetic anhydride; column: Lipodex E, 50 m).